

Clinical practice guidelines for the care and treatment of breast cancer:

7. Adjuvant systemic therapy for women with node-negative breast cancer (2001 update)

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*The Steering Committee is part of Health Canada's Canadian Breast Cancer Initiative.

Abstract

Objective: To assist patients with node-negative breast cancer and their physicians in arriving at optimal decisions regarding treatment.

Evidence: Based on systematic literature review using MEDLINE from 1980 and CANCELIT from 1983 to July 2000. Nonsystematic review of literature was continued through November 2000.

Recommendations:

- Before deciding whether to use adjuvant systemic therapy, the prognosis without adjuvant therapy should be estimated.
- A patient's risk for recurrence can be categorized as low, intermediate or high on the basis of tumour size, histologic or nuclear grade, estrogen receptor (ER) status, and lymphatic and vascular invasion (LVI).
- For each individual, the choice of adjuvant therapy must take into account the potential benefits and possible side effects. These must be fully explained to each patient.
- Pre- and postmenopausal women who are at *low risk* of recurrence can be advised not to have adjuvant systemic treatment. Women who are at low risk, if seeking treatment, may consider tamoxifen.
- Women at *high risk* should be advised to have adjuvant systemic therapy. Chemotherapy should be recommended for all premenopausal women (less than 50 years of age) and for postmenopausal women (50 years of age or older) with ER-negative tumours. Tamoxifen should be recommended as first choice for postmenopausal women with ER-positive tumours. For this last group of patients, further benefit is obtained from the addition of chemotherapy to tamoxifen, but the expected incremental toxicity must also be considered. Whether tamoxifen following chemotherapy should be routinely recommended for premenopausal women with ER-positive tumours is unclear.
- For women at *intermediate risk* with ER-positive tumours, tamoxifen should normally be the first choice. For those who decline tamoxifen, chemotherapy may be considered.

- For most patients over 70 years of age who are at high risk, tamoxifen is recommended for ER-positive tumours. For those with ER-negative disease who are in robust good health, chemotherapy is a valid option.
- There are 2 recommended chemotherapy regimens: (1) 6 cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF); (2) 4 cycles of Adriamycin and cyclophosphamide (AC). More intensive combinations such as CEF (cyclophosphamide, epirubicin and 5-fluorouracil) and AC-Taxol have not yet been evaluated in node-negative disease.
- Tamoxifen should normally be administered at a dose of 20 mg daily for 5 years.
- Patients should be encouraged to participate in therapeutic trials whenever possible.

Validation: The authors' original text was revised by a writing committee, primary and secondary reviewers, and by The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The final document reflects a consensus of all these contributors. External validation of the 1998 guidelines was through the *CMAJ* review process; the current update did not require external review. A writing committee updated the original guideline and then submitted it for further review, revision and approval by the Steering Committee.

Sponsor: The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer was convened by Health Canada.

Completion date: November 2000.

The term "adjuvant systemic therapy" refers to all anticancer medications used after surgical treatment of patients with breast cancer. The 2 forms of adjuvant therapy considered here are chemotherapy (cytotoxic drugs) and hormonal therapy (usually the antiestrogen, tamoxifen). This guideline focuses on adjuvant systemic therapy for women in whom the axillary lymph nodes have been shown to be free of cancer (node-negative disease) (see guideline 4 on axillary dissection). Over half of all patients in whom breast cancer is diagnosed have node-negative disease. Most women who present with node-negative disease are cured by surgery alone.

The use of adjuvant therapy in women in whom the cancer has spread to the axillary nodes (node-positive disease) is addressed in a separate guideline (guideline 8).

The decision to use adjuvant systemic therapy is taken after weighing the benefits of reducing the risk of recurrence against the undesirable side effects and risks of the therapy in question. Since the value placed on different health effects is subjective, the process of weighing potential benefits against potential adverse effects must, to the extent that she wishes to do so, be carried out by the woman herself. To this end, the necessary information, including the uncertainty, must be carefully communicated to the patient in a way that enables her to make a truly informed decision.

This guideline reviews the evidence concerning the risks and benefits of adjuvant systemic therapy for node-negative breast cancer with the objective of assisting patients and their doctors in arriving at optimal treatment decisions. When making the decision of whether or not to administer adjuvant therapy, 3 questions must be considered:

- What is the prognosis for this patient without adjuvant therapy?
- To what extent will the prognosis be improved by the treatment?
- What are the adverse effects of the treatment?

Method

The authors conducted a systematic review of the published literature retrieved from MEDLINE (1980 to July 2000) and CANCERLIT (1983 to July 2000). The terms used were “breast neoplasms,” “node-negative,” “adjuvant,” “chemotherapy,” “hormonal therapy,” “randomized studies” and “prognosis.” The search was restricted to English-language articles. References in review articles and textbooks were also used. A nonsystematic review of the literature on systemic adjuvant therapy for breast cancer and monitoring of major conferences on breast cancer was continued until November 2000. The quality of the evidence on which conclusions were based was categorized into 5 levels (see Levels of Evidence). The iterative process used to develop this guideline has been described previously.^{<1>} A writing committee updated the original guideline and then submitted it for further review, revision and approval by the Steering Committee.

Recommendations

Estimating prognosis without adjuvant therapy

- **Before deciding whether to use adjuvant systemic therapy, the prognosis without adjuvant therapy should be estimated.**

In about 30% of women with node-negative breast cancer who are treated surgically without receiving adjuvant therapy, metastases will eventually develop (level III evidence).^{<2,3>} However, these are average estimates, and the prognosis for patients with lymph-node-negative disease can vary depending on the patient’s age and various tumour characteristics.^{<4>} In addition, the estimate of 30% is based on the outcome of patients in the control (no treatment) arms of clinical trials. Also, one must keep in mind the possibility that the survival rate was influenced by

preferential selection of patients for clinical trials based on poor prognostic features.

Historically, a number of features of the tumour have been used to identify patients at increased risk of recurrence. These include tumour size, histologic differentiation (grade) and hormone receptor status. In addition, the presence of lymphatic and vascular invasion and age less than 35 years have also been found to be associated with an increased risk of recurrence. In recent years, many new predictors of outcome have been reported and are being evaluated for their prognostic value.<5> These include ploidy, S-phase fraction, cathepsin D, heat shock proteins and *HER-2 neu* oncogene overexpression. However, none of these factors has yet consistently been shown to add prognostic information to that associated with the more traditional factors of tumour size, histologic grade and hormone receptor status.<6> In 1996 the American Society of Clinical Oncology recommended that these newer factors not be used to predict recurrence in routine clinical practice.<7> In 1998 an international consensus panel meeting in St. Gallen concluded that the evaluation of risk of recurrence in patients with node-negative breast cancer be categorized on the basis of the patient's age, and on the size, grade and hormone receptor status of the tumour (level IV evidence).<4> More recently, the prognostic and predictive role of *HER-2 neu* overexpression has been studied extensively.<8,9> In the future, knowledge of this status may be more routinely incorporated in the assessment of risk of recurrence and in the choice of treatment.

Tumour size and prognosis

In many studies the size of the tumour at the time of surgery has been found to be an important predictor of recurrence and survival in patients with node-negative breast cancer (level III evidence).<10–19> In most of these studies, size was defined as the maximum diameter of the tumour as estimated from the pathologic specimen. The influence of size on prognosis appears to be a continuum, with tumours less than 1 cm in diameter having a very low risk, which gradually increases as the size of the tumour increases to 3 cm and over. For example, in the control (no adjuvant therapy) group of the International Breast Cancer Study Group trial, the 5-year disease-free survival was as follows: 88% for tumours less 1 cm in diameter, 84% for tumours of 1 cm in diameter, 69% for tumours 1.1 to 2 cm in diameter, 60% for tumours 2.1 to 3 cm in diameter, and 61% for tumours 3.1 to 5 cm in diameter.<15>

Fisher and colleagues reported on the influence of tumour size on outcome in 3 trials.<20–22> Among women with estrogen receptor (ER)-positive tumours, disease-free survival at 5 years for those with tumours less 2 cm in diameter was 75%, compared with 67% for those with tumours 2 cm or greater in diameter. Among patients with ER-negative tumours, disease-free survival was

72% for those with tumours less than 2 cm in diameter and 63% for those with tumours 2 cm or greater in diameter.

In a 10-year follow-up of 382 women with node-negative breast cancer, Rosen and colleagues found that primary tumours 1 cm or smaller in diameter were associated with a recurrence rate of 7% and a cancer-related death rate of 5%.^{<17>} For tumours 1.1 to 2.0 cm in diameter, the recurrence rate was 21% and the cancer-related death rate was 15%. In a similar study, at a mean follow-up of 13.5 years, Quiet and colleagues reported disease-free survival rates of 79% for those with tumours less than 2 cm in diameter and 64% for those with tumours 2 cm or more in diameter.^{<23>}

In a trial conducted in Ontario, over 800 women with node-negative breast cancer who had undergone lumpectomy were randomly assigned to receive or not receive breast irradiation.^{<11>} Tumour size was an independent predictor of mortality. Among women with tumours 2 cm or greater in diameter, compared with those whose tumours were less than 2 cm in diameter, the relative risk of death was 1.4 ($p = 0.03$). Data from the Memorial Sloan-Kettering Cancer Center indicate that women with node-negative tumours less than 3 cm in diameter have a lower relapse rate (28%) than those with tumours 3 to 5 cm in diameter (39%, $p = 0.06$).^{<24>}

In summary, tumour size at the time of surgery is an important independent prognostic factor. Although no precise size can be identified that differentiates high risk from low risk of recurrence or death, many studies have used a diameter of 2 cm as a cutoff point.

Histologic and nuclear grade and prognosis

An association between grade and outcome has been reported in a number of studies. Depending on the study, either histologic or nuclear grade, or both, have been evaluated.^{<11,15,19,25>} There is a high degree of concordance between histologic grade and nuclear grade.^{<25>}

Although there is some interaction between grade and other variables, multivariate analyses show grade to be an important independent predictor. The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted an analysis of 950 patients with node-negative breast cancer who did not receive adjuvant systemic therapy in trial B-06.^{<22,25>} The 5-year disease-free survival of patients with good nuclear grade (well differentiated and moderately well differentiated) was 80%, compared with 64% for patients with poor grade (poorly differentiated) ($p < 0.01$). With regard to histologic grade, the 5-year disease-free survival was 83% for those with tumours of good histologic grade, compared with 67% for those with tumours of poor histologic grade ($p < 0.01$). In the Cox model, good nuclear grade was an independent predictor of disease-

free survival (good grade RR = 0.76, $p = 0.01$).

In the radiotherapy trial conducted in Ontario involving women with node-negative breast cancer, nuclear grade was an independent predictor of mortality.^{<11>} For those with tumours of poor nuclear grade (grade 3) versus all others, the relative risk was 2.0 ($p = 0.0001$).

In a trial conducted by the International Breast Cancer Study Group, women with node-negative breast cancer were randomly assigned to receive perioperative adjuvant chemotherapy or no adjuvant treatment.^{<15>} Among the 388 patients in the control group, the 5-year disease-free survival for those with histologic grade 1 tumours was 89%, grade 2 tumours 65% and grade 3 tumours 60%. In a Cox model the relative risk of recurrence for grade 3 compared with grade 1 tumours was 1.74 ($p = 0.02$).

Several different grading systems have been reported in published series, but in Canada most pathologists use a modification of the Bloom Richardson grading system to evaluate the histologic grade.^{<26>} This grading system is based on tubule formation, nuclear pleomorphism and mitotic index. Each score is added to give a combined score of 3 to 9: 3 to 5 points indicates grade 1 or well differentiated, 6 to 7 points indicates grade 2 or moderately differentiated, and 8 to 9 points indicates grade 3 or poorly differentiated. Since a pathologist's subjective judgement is involved when reporting on grade, there is potential concern regarding reproducibility. However, several studies have shown a high degree of interobserver agreement when evaluating histologic grade.^{<27,28>}

In summary, the prognosis for patients with grade 1 tumours is considered good, whereas the prognosis for those with grade 3 tumours is considered poor. It is unclear whether patients with grade 2 tumours have an intermediate prognosis or should be grouped prognostically according to grade 1 or grade 3 tumours.^{<15,26>}

Hormone receptor status and prognosis

The influence of hormone receptor status on outcome is weaker than that of tumour size or histologic or nuclear grade and has been demonstrated less consistently.^{<29>} A follow-up of 8530 women from the San Antonio database showed a small but statistically significant increase (9%) in disease-free survival at 5 years for patients with ER-positive tumours, compared with those with ER-negative tumours (level III evidence).^{<29,30>} Indirect comparison of the control groups of the NSABP B-13 and B-14 trials also suggests a slightly better survival and disease-free survival for women with ER-positive tumours than for those with ER-negative tumours (level III evidence).^{<20,21>} The use of estrogen and progesterone receptor status to predict recurrence was recommended by the American Society of Clinical Oncology in 1996.^{<7>} The prognostic value of

ER status based on immunohistochemical techniques is now accepted.<31>

Age and prognosis

A patient's age appears to correlate with outcome. Patients less than 35 years of age appear to have, on average, a poorer prognosis than older patients, and this has been used as a prognostic indicator.<4,18,32,33> However, the relationship is poorly defined and difficult to distinguish from the influence of menopausal status and other tumour features. At present, there is insufficient evidence to justify the incorporation of age as an independent prognostic factor.

Lymphatic and vascular invasion (LVI) and prognosis

In several studies of patients with node-negative disease, a relationship has been found between invasion of lymphatic and blood vessels and increased recurrence or reduced survival.<14,15,17,19,24,34–38> In 4 studies, invasion was found to be an independent prognostic factor by multivariate analysis.<13,16,32,39> However, not all studies have found such an association, and its practical value as a prognostic factor is diminished by the fact that it can be difficult to evaluate and may have poor reproducibility.<40–42>

In summary, there is good evidence that small tumour size (less than 1 cm in diameter), low nuclear grade (grade 1) and ER positivity are favourable prognostic factors. In contrast, large tumour size (greater than 2 cm diameter), high nuclear or histologic grade (grade 3), ER negativity, and lymphatic and vascular invasion are unfavourable prognostic factors.

- **A patient's risk for recurrence can be categorized as low, intermediate or high on the basis of tumour size, histologic or nuclear grade, estrogen receptor (ER) status, and lymphatic and vascular invasion (LVI).**

In the following classification, the risk of recurrence associated with certain combinations of features can be estimated with some confidence on the basis of level III evidence. The risk associated with other combinations, which have not been adequately studied, must be based on level V evidence. With this proviso, patients can be categorized somewhat arbitrarily into 3 levels of risk as outlined below.

Low risk: A low-risk category is defined by tumour diameter of 1 cm or less with *all* prognostic factors favourable (grade 1, ER positive, no LVI). There are many oncologists who would also include in this category a patient with a tumour less than 2 cm in size and *all* other factors favourable. The risk of recurrence at 10 years associated with this low-risk category is less than 10% (level III evidence).<2–4,24>

High risk: A patient with a tumour more than 3 cm in diameter, *irrespective* of any other factors, should be considered at high risk (level III evidence). In addition, a patient with a tumour more than 1 cm in diameter, associated with *any* other unfavourable prognostic feature (grade 3, ER negative or LVI) should also be considered at high risk for recurrence (level V evidence). For those in the high-risk category, the risk of recurrence within 5 to 10 years is at least 20% and in some circumstances as high as 50%.<2–5,11>

Intermediate risk: There are insufficient data on the natural history of tumours with other combinations of risk factors to predict outcome. On the basis of level III evidence, patients in the intermediate risk category face a probability of recurrence at 10 years of 10% to 20%.<4,5>

Adjuvant systemic therapies

Chemotherapy

There is good evidence that chemotherapy will result in a small but definite increase in disease-free and overall survival of patients with node-negative breast cancer.<2> Several randomized trials in which chemotherapy was specifically evaluated in patients with node-negative disease have each demonstrated a benefit (level I evidence). These are summarized below.

In the Milan trial, 90 patients with node-negative breast cancer and ER-negative tumours were randomly assigned to receive a 9-month course of intravenous cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or no treatment.<43> At 12 years, the relapse-free survival rate was significantly higher in the treated group (71%) than in the control group (43%) ($p = 0.007$). Similar results were observed with regard to overall survival (80% in treated patients v. 50% in the control group, $p = 0.006$). However, in this trial the outcome of the patients in the control group was much poorer than is usually observed; thus, these findings should be generalized with caution.

In a trial conducted by the International Breast Cancer Study Group (formerly the Ludwig group), 1275 women with node-negative breast cancer were randomly assigned to receive a 1-month course of adjuvant CMF or no treatment.<44> The 5-year disease-free survival rate was slightly but significantly better in the chemotherapy group than in the control group (74% v. 68%, $p = 0.02$). In the NSABP B-13 trial, 679 patients with node-negative breast cancer and ER-negative tumours were randomly assigned to receive sequential methotrexate and fluorouracil (MF) or no treatment.<22> At 8 years, disease-free survival in the chemotherapy group was 74%, compared with 59% in the no-treatment group ($p < 0.001$). In a follow-up study the NSABP B-19 trial

compared sequential MF with CMF for node-negative, ER-negative tumours.<21> At 5 years, an overall disease-free advantage (82% v. 73%, $p < 0.001$) and a borderline survival advantage (88% v. 85%, $p = 0.06$) were evident with CMF. The advantage of CMF was greater among women less than 50 years of age than among those 50 and older.

The NSABP B-23 trial compared chemotherapy with or without tamoxifen in women with node-negative, ER-negative tumours.<45> Patients were randomly assigned to receive CMF, CMF with tamoxifen, doxorubicin and cyclophosphamide (AC), or AC with tamoxifen. No differences in disease-free survival or overall survival were observed between the groups. Thus, AC was equal to CMF, and tamoxifen did not add any benefit in these patients with ER-negative tumours.

In the Intergroup trial, 406 women with either ER-negative tumours or tumours larger than 3 cm in diameter were randomly assigned to receive either CMF with prednisone (CMFP) or no treatment.<46> There was a statistically significant increase in the 10-year disease-free survival in the chemotherapy group compared with the control group (73% v. 58% respectively, $p = 0.0006$) and in overall survival (81% v. 71% respectively, $p = 0.02$).

In 1995 the Early Breast Cancer Trialists' Collaborative Group conducted a meta-analysis of 47 trials to evaluate adjuvant polychemotherapy in 18 000 women with early-stage breast cancer.<2> Although different chemotherapy regimens were used in the trials, CMF was among the more common ones. Few women aged 70 or older were included in these studies. Among women less than 70, after standardization for age and time since randomization, the proportional reductions in risk were highly statistically significant and similar for node-negative and node-positive disease. Chemotherapy resulted in a proportional reduction in recurrence of 35% (standard deviation [SD] 4%) among women less than 50 years of age and 20% (SD 5%) among women aged 50–69. For survival the reductions were 27% (SD 5%) among women less than 50 and 11% (SD 3%) among women aged 50–69. For women with node-negative disease, these proportional reductions in mortality translated into absolute survival benefits at 10 years of 7% (71% v. 78%) for women less than 50 and 2% (67% v. 69%) for women aged 50–69. In the direct comparison of anthracycline-containing chemotherapy versus non-anthracycline-containing chemotherapy, there was a suggestion of benefit for the former, with a further 12% proportional reduction (SD 4%) in recurrence and a further 11% reduction (SD 5%) in mortality.

Tamoxifen

There is good evidence that tamoxifen will result in a small but definite increase in disease-free and overall survival among patients with node-negative breast cancer.<3> There is level I evidence that ovarian ablation, whether induced by surgery or radiotherapy, is associated with

significant improvement in recurrence-free and overall survival among women less than 50 years of age at the time of treatment.<47> Although ovarian ablation is now rarely used, a number of trials have evaluated tamoxifen in women with node-negative breast cancer.

In the NATO trial, there were 300 women with node-negative disease who received tamoxifen and 305 women who received no treatment.<48> At a median 5.6 years, there were 80 recurrences in the tamoxifen group and 107 in the control group, a benefit comparable to the statistically significant difference observed in the combined node-negative and node-positive population.<48>

In the Scottish study of 747 women with node-negative disease, there was a statistically significant difference in disease-free survival in favour of tamoxifen at 5 years (relative risk reduction of 0.6, $p = 0.0001$).<49> In the NSABP B-14 trial, 2844 women with node-negative, ER-positive tumours were randomly assigned to receive tamoxifen for 5 years or no treatment.<20> The disease-free survival rate with tamoxifen was 82%, compared with 72% in the control group ($p < 0.000005$). In both the NSABP and Scottish trials no difference was detected in overall survival between treatment groups.

The Early Breast Cancer Trialists' Collaborative Group analyzed the data for over 35 000 women enrolled in 54 clinical trials.<3> The group reported in 1998 that, in trials in which tamoxifen was given for about 5 years, women with ER-positive disease had a proportional reduction in recurrence of 47% (SD 3%) and a proportional reduction in mortality of 26% (SD 4%). The absolute improvement in the 10-year recurrence rate was 14.9% (SD 1.4%) among women with node-negative disease compared with control subjects, and was very similar to the absolute improvement of 15.2% (SD 2.5%) among women with node-positive disease. Women with node-negative, ER-positive disease had a 10-year absolute improvement in survival of 5.6% (SD 1.3%, $p < 0.00001$) when they received 5 years of tamoxifen. These benefits appeared to be largely irrespective of age, menopausal status and use of chemotherapy. Five years of tamoxifen was superior to shorter durations of treatment. No benefit regarding recurrence or survival was detected in women with ER-negative tumours. The NSABP B-23 trial also showed no benefit from tamoxifen in ER-negative tumours.<45>

Fisher and colleagues reported the results of the NSABP B-20 trial, in which 2363 women with ER-positive, node-negative breast cancer were randomly assigned to receive tamoxifen, tamoxifen plus MF or tamoxifen plus CMF.<50> There was a statistically significant improvement in 5-year disease-free survival in favour of chemotherapy plus tamoxifen over tamoxifen alone: the disease-free survival rates were 85% with tamoxifen alone, 90% with tamoxifen plus MF and 89% with tamoxifen plus CMF.<50>

Adverse effects of adjuvant systemic therapy

Adjuvant chemotherapy frequently causes acute adverse effects (level III evidence)

Nausea, vomiting and diarrhea are common.<51> The nausea and vomiting are generally well controlled with antiemetics.<52> Fatigue is also a common accompaniment of all chemotherapy regimens. Some weight gain may occur in approximately 14% of women receiving CMF regimens.<53> Complete but temporary alopecia occurs in approximately 40% of patients receiving CMF<53> and in virtually all patients receiving doxorubicin.<54> In the NSABP B-15 study, anthracycline-containing chemotherapy (doxorubicin) was associated with more vomiting and more frequent and more complete alopecia than were CMF regimens, but the latter caused more nausea.<54> Febrile neutropenia occurs infrequently and may require hospitalization in 1% to 2% of patients.<55> Permanent amenorrhea occurs in approximately 70% of patients but is less common in younger than older women.<56,57> Venous thromboembolism, which can be life-threatening and require anticoagulant therapy, may occur in 2% to 7% of patients.<53,58> There is a risk of cardiac injury with anthracycline-based chemotherapy, but clinically important toxicity is rare (below 1%) with conventional adjuvant doses.<54,59,60> In a review of 133 randomized trials, fatal toxicity varied from 0.1% to 1.0%.<1>

All chemotherapy is potentially leukemogenic. In a recent review of a series of adjuvant trials in Milan involving CMF, 3 cases of leukemia were observed in 2465 patients (the cumulative absolute risk at 15 years was 0.23%).<61> The NSABP reported 2 cases of leukemia in 1562 patients within 18 months of starting treatment with standard-dose AC.<62> Monitoring of these patients is continuing. If such therapies are leukemogenic, the level of risk must be low.

Tamoxifen is associated with relatively few severe side effects (level II evidence)

About 20% of women taking tamoxifen experience severe hot flashes, which abate with time.<53> Tamoxifen probably causes occasional depression, but evidence regarding this complication is conflicting (level IV evidence).<63> A more serious complication, venous thromboembolism, is slightly increased in those taking tamoxifen (1.3%) compared with those not taking it (0.1%) (level I evidence).<22> Use of tamoxifen has also been reported to be associated with an increased risk of cataract (“posterior subcapsular opacities”) in the NSABP B-14 study and with an increased risk of cataract surgery in the BCPT trial.<64> In general, for most complications, the risk of toxicity is increased by the concurrent use of chemotherapy with tamoxifen in postmenopausal women.<65>

Several studies have reported a small but significant increase in the risk of endometrial cancer (level I evidence).^{<66–68>} In the NSABP B-14 study, after 5 to 8 years of follow-up, the annual risk of endometrial cancer for women who received tamoxifen was 1.6/1000, compared with 0.2/1000 for those who did not.^{<66>} Thus, women taking tamoxifen should be warned to report any vaginal bleeding promptly. In none of these trials was any increase in the incidence of other solid tumours detected.^{<66–68>}

Choosing adjuvant therapy: factors predictive of benefit

- **Menopausal status and ER status influence the response to systemic adjuvant therapy**

Postmenopausal status is defined as starting 1 year after the last period or, if menopausal status cannot be determined, after the age of 50 years. Most evidence concerning the influence of ER and menopausal status (or age) on response to therapy is based on studies involving women with metastatic breast cancer or node-positive disease (see guideline 8). Previously untreated patients with stage IV breast cancer have at least a 50% chance of responding to tamoxifen if the ER status is positive, compared with a less than 10% response rate if the ER status is negative (level I evidence).^{<69>}

Evidence based on studies involving women with node-negative disease is more sparse. In the overview analysis, chemotherapy was associated with a risk reduction for recurrence and mortality in all age groups, but the greatest effect was in the women who were under 50 years of age. Conversely, the greatest effect of tamoxifen was found in women over 50 years of age.^{<2,3>}

Evidence of a relation between tamoxifen response and ER status in patients with stages I and II breast cancer comes from the overview analysis.^{<2,3>} Among patients with ER-negative tumours no benefit in recurrence or survival rates was seen, although contralateral breast cancer incidence was reduced. The question of whether tamoxifen might actually be detrimental in ER-negative tumours has been raised by a subset analysis of an Intergroup trial of CMF versus CAF with or without tamoxifen in high-risk node-negative breast cancer patients.^{<70>} The addition of tamoxifen was associated with a worse outcome in the premenopausal ER-negative subset (disease free survival 88% for chemotherapy v. 83% for chemotherapy with tamoxifen, overall survival 94% and 89% respectively).^{<70>} The results of this subset analysis can be considered only as hypothesis generating and deserve further investigation.

- **For each individual, the choice of adjuvant therapy must take into account the potential benefits and possible side effects. These must be fully explained to each patient.**

The evidence on which to base therapeutic choices is incomplete. In making decisions based on the available evidence, women must personally evaluate the potential gains and side effects of each option, which must be presented clearly so as to help patients make these difficult choices. At present, options are best given in terms of the absolute rather than the relative risk involved. Presentation of these options is demanding and requires time. Visual aids such as a “decision board” and written material may be useful in this process.<71>

Suggested therapeutic approaches according to risk category, age and ER status are summarized in the following section.

Recommended therapies

Low risk

- **Pre- and postmenopausal women who are at *low risk* of recurrence can be advised not to have adjuvant systemic treatment. Women who are at low risk, if seeking treatment, may consider tamoxifen.**

Patients in the low-risk category have a recurrence rate of less than 10% over 10 years. With an approximately 26% reduction in recurrence after therapy,<2,3> they may expect a reduction in the absolute recurrence rate of between 1% and 2%. Thus, not more than 2 of every 100 women estimated to be at low risk of recurrence will benefit from treatment, which is a small benefit in relation to the potential toxicity. Therefore, systemic adjuvant therapy should not be recommended for such women.<4> Women who desire some form of treatment can be considered for tamoxifen since all have ER-positive tumours.

High risk

- **Women at *high risk* should be advised to have adjuvant systemic therapy.**
- **Chemotherapy should be recommended for all premenopausal women (less than 50 years of age) and for postmenopausal women (50 years of age or older) with ER-negative tumours.**
- **Tamoxifen should be recommended as first choice for postmenopausal women at *high risk* with ER-positive tumours. For this last group of patients, incremental benefit is obtained from the addition of chemotherapy to tamoxifen, but there is more toxicity with chemohormonal therapy than with tamoxifen alone. Therefore, the risks and benefits of chemotherapy should be discussed with the patient in making a treatment decision for tamoxifen alone or with chemotherapy.**

- **Whether tamoxifen should be routinely recommended after chemotherapy in premenopausal women with ER-positive tumours is unclear.**

It is estimated that adjuvant systemic therapy will reduce the 10-year recurrence rate by approximately 26%.<2> Thus, for every 100 women with a background (untreated) recurrence rate of 20%, 5 may benefit from adjuvant systemic therapy. If the background rate were 50%, 13 women might benefit from such treatment. There are no trials that have directly compared the efficacy of chemotherapy and tamoxifen in women with node-negative disease, but there is sufficient indirect evidence based on the overview and on the node-positive trials cited above to support these recommendations.

In a recent trial involving women with node-negative, ER-positive tumours (NSABP B-20), the combination of chemotherapy plus tamoxifen was reported to result in a better disease-free survival than tamoxifen alone.<50> Combined therapy may become the preferred option for such patients in the future.

In the most recent overview analysis, women who received chemotherapy plus 2 years of tamoxifen had a 22% (SD 4%) reduction in mortality compared with those who received chemotherapy alone.<2> The corresponding data for chemotherapy plus 5 years of tamoxifen versus chemotherapy alone were 52% (SD 8%) and 47% (SD 9%) respectively. Among women less than 50 years of age the reduction in recurrence was 40% (SD 19%) and the reduction in mortality 39% (SD 22%) in the presence of chemotherapy. For this subgroup the data are not reliable because of the relatively small number of patients (level II evidence). Hence, although the results suggest that the addition of tamoxifen to chemotherapy may have improved results compared with chemotherapy alone, the results are not conclusive. A recently completed trial of the National Cancer Institute of Canada Clinical Trials Group (MA12) addressed this issue; premenopausal women with node-positive or node-negative breast cancer who completed adjuvant chemotherapy were randomly assigned to receive either tamoxifen or placebo. Results are not yet available from this trial.

Intermediate risk

- **For women at *intermediate risk* with ER-positive tumours, tamoxifen should normally be the first choice. For those who decline tamoxifen, chemotherapy may be considered.**

Available evidence suggests that for women at intermediate risk, the benefit expected from chemotherapy is not substantially greater than that from tamoxifen, especially for women with ER-positive tumours. (In the absence of evidence, women with ER-negative tumours are usually treated as being at “high risk.”) Since chemotherapy is associated with higher morbidity, tamoxifen

is the recommended first-line therapy. Although the option of ovarian ablation is rarely used, it may be an alternative to tamoxifen for premenopausal women. Chemotherapy plus tamoxifen is more effective than tamoxifen alone, but the incremental benefit is small. Discussion with the patient of risks and benefits is required.

- **For most patients over 70 years of age who are at high risk, tamoxifen is recommended for ER-positive tumours. For ER-negative tumours, chemotherapy is a valid option for women who are in robust good health.**

There is little evidence to guide the choice of therapy for women over 70 years old. With increasing age or frailty, chemotherapy is less well tolerated. However, tamoxifen, which is well tolerated, can be recommended for ER-positive tumours.

Optimal adjuvant regimens

- **There are 2 recommended chemotherapy regimens: (1) 6 cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF); (2) 4 cycles of Adriamycin and cyclophosphamide (AC). More intensive combinations such as CEF and AC-Taxol have not yet been evaluated in node-negative disease.**

There are 2 trials that compared anthracycline-containing chemotherapy with CMF for node-negative disease.<45,70> In the Intergroup study of high-risk node-negative breast cancer, CAF was marginally superior to CMF for both the 5-year disease free survival (92% v. 90%) and the overall survival (85% v. 82%); there was more toxicity with CAF than with CMF.<70> In the NSABP B-23 trial, there was no difference between AC and CMF for node-negative, ER-negative tumours.<45> The course of AC is shorter in duration and has a different toxicity profile than that of CMF. However, there is the concern of cardiomyopathy and leukemia with AC. More intensive combinations such as CEF or AC-Taxol have not yet been tested directly in node-negative disease, but an ongoing National Cancer Institute of Canada Clinical Trials Group trial (MA21) is addressing this issue.

- **Tamoxifen should normally be administered daily for 5 years.**

There is level I evidence that therapy with tamoxifen should be continued for more than 2 years and not more than 5 years. In a trial conducted by the Swedish Breast Cancer Cooperative Group, 3887 postmenopausal patients with node-positive or node-negative breast cancer were randomized to receive tamoxifen for either 2 years or 5 years.<72> At a median follow-up of 5 years, there was a significant improvement in both disease-free and overall survival in favour of the longer treatment. The survival at 10 years was 80% in the group who received tamoxifen for 5

years, compared with 74% in the group who received tamoxifen for 2 years ($p = 0.003$). The Early Breast Cancer Trialists' Collaborative Group, in its overview analysis,³ demonstrated greater benefits when tamoxifen was given for 5 years than when it was given for shorter duration.

There is also level I evidence that no benefit can be expected for continuing tamoxifen treatment longer than 5 years. In the NSABP B-14 trial, 1172 women with node-negative, ER-positive tumours who had received tamoxifen for 5 years were randomly assigned to continue tamoxifen for 5 more years or to stop treatment. There was no statistically significant difference in the 4-year disease-free survival (86% for 10-year tamoxifen v. 92% for 5-year treatment) nor in the overall survival (94% v. 96% respectively).⁷³ The Scottish tamoxifen trial showed a similar outcome. In this trial, 342 postmenopausal women with node-positive breast cancer who had received tamoxifen for 5 years were randomly assigned to receive tamoxifen for an additional 5 years or to stop therapy. At a median follow-up of 6.2 years, the disease-free survival among those who received tamoxifen for 5 years was 70%, compared with 62% among those who received tamoxifen for 10 years.⁷⁴

Clinical trials

- **Patients should be encouraged to participate in therapeutic trials whenever possible.**

Significant advances in the management of women with early stage breast cancer have occurred because of the results of clinical trials of adjuvant therapy. Improvement in the care of future patients with breast cancer is thus dependent on the participation of sufficient numbers of patients in such trials. Physicians treating patients with breast cancer should therefore be aware of currently available trials, and the option of participation should be offered to patients.

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